

patients of these two groups as well as in others. The "normal" for the individual patient was established before the operation. Variations were studied on the evening of the operation day and on the following day.

Allowing for all the possible factors which might influence these tests, we failed to find any striking differences between the sodium amytal and the scopolamin groups. There is a marked drop from the accepted "normal" on the day of operation in both groups, which is slightly greater in the sodium amytal group. The dissimilarity between the groups is so small that it must be disregarded, particularly so since on the day after operation the sulphophenolphthalein excretion approaches the accepted "normal" with equal promptness in both groups.

## II. ITS USE IN PREGNANCY GROUP

We have studied the sulphophenolphthalein excretion in pregnant women during and following labor in twenty controls and twenty-one sodium amytal patients. The latter received from six to seven and one-half grains intravenously in the advanced first stage of labor, followed by supplementary nitrous oxid analgesia during the second stage. For obvious reasons studies of fluid intake and output were unsatisfactory and therefore discontinued. A comparison of the two groups studied here indicates that sodium amytal in the dosage given does not influence the glomerular activity of the kidney as expressed in per cent of sulphophenolphthalein excretion.

## CONCLUSIONS

Sodium amytal and morphin, when given in sufficiently large doses to produce prolonged hypnosis, seems to allow a greater fluid intake by surgical patients on the day of and the day following the operation when compared to a similar group of patients having received scopolamin and morphin. On the other hand, urinary output is actually and relatively decreased in the sodium amytal group, more marked on the day of operation, but in neither case sufficiently marked to constitute a potential danger to the patient. It is interesting that in some instances output rises over intake in scopolamin patients twenty-four hours ahead of sodium amytal patients.

Sulphophenolphthalein excretions observed in a similar study are so slightly, if at all, influenced by sodium amytal that we may disregard the difference. Similarly, the results of this test during and after labor show no changes in sulphophenolphthalein excretions in patients having received from five to seven and one-half grains of sodium amytal intravenously.

We may therefore conclude that sodium isoamylethyl barbiturate when given orally or intravenously, while it apparently depresses urinary output, does not constitute a menace in the patient whose kidney function is otherwise normal.

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## TRIBROMETHANOL AS A PREOPERATIVE NARCOTIC\*

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TRIBROMETHANOL was discovered by Willstaetter and Duisberg during the reduction of bromal at the I. G. Farben-Industrie, Elberfeld, and was called by them "Avertin" or "E-107" as a trade mark. Chemically it is ethyl alcohol with three bromin atoms introduced into the formula or  $\text{CBr}_3\text{-CH}_2\text{-OH}$ , and should be called tribromethyl alcohol or tribromethanol.<sup>1</sup> The substance itself is a white crystalline powder which is soluble in water up to  $3\frac{1}{2}$  per cent at 37 to 40 degrees Centigrade. At a higher temperature the drug is decomposed, breaking down into hydrobromic acid and dibromacetaldehyd. This latter substance is highly injurious to the intestinal mucosa. Care must be taken in preparing the mixture that the water is not warmed over 40 degrees Centigrade. In all of the early experimental work the drug in powder form was used, and as quite a few deaths were reported, it was decided to dispense it in liquid form, thus simplifying the technique of preparation and lessening the danger of errors in weighing out the individual dosages. The so-called "Avertin-Fluid" is a solution of tribromethanol in amylene hydrate (itself a narcotic); one cubic centimeter of the "fluid" contains one gram of tribromethanol. This solution is extremely sensitive to air, light and heat, and must be kept tightly corked in dark bottles.

## REPORTS ON TRIBROMETHANOL

After tribromethanol was discovered, it was subjected to tests and experimentation on animals before any use of it was made in human beings. The drug was then given out to different clinics for experimental use and was not available generally until one hundred thousand cases had been reported. The great mass of literature available on the subject is therefore largely in German. During the last year several articles have appeared in the English and Irish literature, but as yet no report on administration of the drug or a series of cases has appeared in American literature. It is because of the newness of the drug and the scarcity of reports in this country that we dare report so small a series as twenty-five cases, knowing full well that no true statistics can be tabulated therefrom, and only the general conclusion of caution drawn.

The early reports were full of enthusiasm for the drug not only as a narcotic but as an anesthetic. Subsequent reports bear more and more the note of caution. At the present time it is apparently agreed that the drug should be used as a "basal anesthetic" to obtain preoperative narcosis only, and should not be relied upon as the sole anesthetic agent. The danger of a fatal out-

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come is too great when the dosage is increased and the administration pushed to complete anesthesia.

#### DOSAGE AND ACTION

The dosage of the drug is calculated on the body weight of the patient in kilograms, and most of the reports from the continent advocate from 100 to 150 milligrams per kilogram. We feel that these figures are unnecessarily high, for Anschutz<sup>2</sup> mentions the report of a death within thirty minutes after a dosage of 125 milligrams per kilogram, while McWilliams and Wilson<sup>3</sup> report a death with a dosage of only 100 milligrams per kilogram. On the other hand, there are reports of apparent safety with dosages as high as 175 milligrams per kilogram. In our small series we have set 90 milligrams per kilogram as a maximum dosage with 80 milligrams per kilogram as average and have had satisfactory results, using as low as 70 milligrams per kilogram. In this day and age of safe anesthesia one death in ten thousand administrations is nothing short of criminal, and no drug or dosage of a drug should be used that will increase that percentage. Morrin,<sup>4</sup> desiring to obtain complete anesthesia, advocates the administration of the drug by fractional dosage. He starts with 100 milligrams per kilogram and, if sensitive to pain, in fifteen minutes gives a further dosage of 25 milligrams per kilogram, and states that in practically every instance this dosage is sufficient. If in ten minutes more the patient is not anesthetic an additional 25 milligrams per kilogram may be added. This maximum should be required but rarely, and should never be exceeded. However, in our opinion, his initial dose is too high and the practice of giving additional small doses is dangerous.

Tribromethanol has been used intravenously and by mouth, but experience has shown that when it is given by rectum the best results are obtained. It is very rapidly absorbed by the mucous membrane, being much more rapidly absorbed than the water in which it is in solution. So rapidly in fact that 80 per cent of it is gone in the first twenty minutes and 95 per cent in two hours. In from six to ten minutes the patient becomes very drowsy and drops into a deep sleep, without any stage of excitement. The blood pressure may fall a few points and the breathing become more shallow. Cyanosis may be noted, but is thought to be due to the falling back of the tongue since if an airway is inserted or the chin held up, cyanosis does not occur. Some German reports state that cyanosis is the rule and may be due to the larger dosage used, or to the fact that morphin was used in combination, for we did not notice cyanosis in our series.

After being absorbed from the rectum, tribromethanol is present in the blood, becomes detoxicated by combining with glycuronic acid in the liver and is eliminated as such by the kidneys. Straub, as reported by Guttman,<sup>5</sup> recovered 81 per cent of the administered drug in the urine

and traces of bromin were found in the perspiration, but none were found in the feces or in the expired air. Because of the detoxication of the drug in the liver, its use in organic liver disease is contraindicated. There seems, however, to be considerable discussion concerning its use in obstructive jaundice and many authors feel that the mere presence of icterus is not necessarily a contraindication. With its elimination by the kidneys a transient irritation occurs, and hyaline casts and red cells appear in the urine. Though they disappear completely in a few days, this result is a sufficient cause for contraindication to its use in kidney disease. It is not, in the least, eliminated by the lungs and no untoward effects have been demonstrated in the lungs. Tribromethanol is, therefore, recommended in lung surgery and for operative patients suffering from tuberculosis.

At first no means of speeding the detoxication of the drug was known. The bromin is in an organic combination in the molecule and cannot be reached or detoxicated by the administration of chlorids. It was later noted that patients suffering from hyperthyroidism withstood large doses very well and awoke from moderate dosages much more rapidly than the ordinary patients. It was suggested by Lendle, Bromfield, Shipway<sup>6</sup> and Edwards<sup>7</sup> that the administration of thyroxin to patients who slept overlong might aid in the elimination of the drug. Pribham<sup>8</sup> reports gratifying results in the use of thyroxin and at present this is the only known antidote, if such it may be called.

#### EFFECTS ON VARIOUS SYSTEMS AND ORGANS OF THE BODY

One of the early effects noted was an irritation of the rectal mucosa, apparently not due to tribromethanol itself but to a faulty preparation of the mixture and to overheating of the water which caused the production of dibromacetaldehyd. Aside from the factor of irritation of the mucosa it is probably wiser not to use the drug in ulcerative colitis, severe hemorrhoids or in carcinoma of the rectum, because it is even more rapidly absorbed from a raw area.

The respiratory center may quite frequently be affected, the respirations may decrease in number but usually are slightly increased and become more shallow in excursion. The smaller the dosage the less effect is seen and all who reported respiratory embarrassment used a dosage of 100 milligrams per kilogram or more. If the dosage is pushed far enough, respiratory paralysis and death ensue. When morphin is used in conjunction with tribromethanol, the respiratory change is more marked. Respiratory embarrassment should be treated with the administration of carbon dioxid. Because of this effect on the respiratory center we do not recommend its use in brain surgery.

A reduction in blood pressure is noted directly after the injection and comes on with the relaxation and deep sleep of the patient. With the dosages that we have used this drop has never been

alarming, representing only the normal drop of physiological sleep and the elimination of psychic factors. When supplemental anesthetic agents were started and the operation commenced the blood pressure again assumed the former level and maintained it throughout the operation. On an average the drop in systolic pressure was from 15 to 20 millimeters. Should the drop in blood pressure become alarming, caffein and ephedrin may be used.

Though it is stated in the experimental work that no effects were noted in the heart, pulse rate or blood pictures, there has been one death reported, with fatty degeneration of the liver, heart, and kidneys. In large doses tribromethanol, like ether and chloroform, produces acidosis (Killian<sup>9 10</sup>).

#### PROCEDURE AND TECHNIQUE

On the continent there is a difference of opinion concerning the use of morphin with tribromethanol; some clinics recommend from one-sixth to one-third grain of morphin, or its equivalent in some other form of opium, and some recommend that no morphin be used at all. No enema is given the morning of the operation because some fluid may be retained and could thus dilute the dosage intended or the rectal mucosa could become irritated. In twenty minutes to a half-hour the operation can be started and a small amount of supplemental anesthesia be used. In Europe, ether is most often chosen and the amount necessary is very much less than is required in any other type of combined anesthesia. Frequently the patients sleep 24-48-72 hours and experience no postoperative pain, nausea, or vomiting.

In our series we did not use any form of morphin or any of the lesser hypnotics, as we wished to find out the true value of the tribromethanol unaided by other drugs. To illustrate the procedure in detail: For a patient weighing 65 kilograms, to whom we desire to give 80 milligrams per kilogram, the dosage of tribromethanol would be 5.2 grams or 5.2 cubic centimeters of the "Avertin-Fluid." This amount is accurately measured in a pipette and put into a flask containing 173 cubic centimeters of distilled water which has been heated to 38 to 40 degrees Centigrade. The flask is vigorously shaken for about a minute until the mixture (a three per cent solution of tribromethanol in distilled water) is in solution. A few cubic centimeters are then removed and tested with a few drops of 1:1000 solution of Congo red. If the color remains red, the solution is suitable for injection. If the slightest tinge of blue color appears, the tribromethanol has decomposed and the solution must be discarded, for hydrobromic acid and dibromacetaldehyd are present. Being careful that the solution does not cool below 37 degrees Centigrade, the mixture is poured into a large triumph syringe connected to a rectal tube and is injected into the rectum. The rectal tube may be left *in situ* if desired and a clamp placed

on it, so that, should any untoward effects be noted, the clamp can be released, the solution withdrawn and the rectum irrigated with water. However, the rate of absorption is so fast that by the time any bad effects are noted most of the tribromethanol has disappeared from the rectum. Nevertheless it has been noted that the after-sleep can be shortened by removing from the rectum that small portion still unabsorbed at the end of the operation. In about six to ten minutes the patient becomes very drowsy, yawns, stops talking, and has the appearance of being unable to stave off sleep any longer. The patient in his bed is taken to the operating room, and often will rouse a bit when transferred to the operating table and, if questioned, may answer quite rationally. While the surgical field is being prepared he may attempt to draw away from the cold alcohol and will always move if a hypodermoclysis is started. Before the actual surgery is commenced, nitrous oxid and oxygen is started, in every case in our series the oxygen percentage being maintained at 18, 20, or 25 per cent; the color throughout was always the brightest pink and at no time was the slightest cyanosis allowed to appear. The blood pressure was taken at the time the injection was made; and in many of the cases after sleep or the drowsy state appeared, it showed a drop of from 10 to 20 millimeters of mercury, but after the establishment of the nitrous oxid-oxygen and the operation was begun, the blood pressure was back to the former level and remains so throughout the operation. In only one instance did the respiratory rate drop and with this patient it was reestablished at the normal rate when the operation started. On the other hand, most of the patients showed an increase in respiratory rate with some slight diminution in excursion. No effect was noted on the pulse rate. Six of our patients did not appear to go to sleep before going to the operating room. They were somewhat drowsy but continued to talk until the nitrous oxid was started, yet not one of them remembered anything beyond a few moments after the injection.

#### COMMENTS ON SERIES REPORTED

Our series is as limited as it is because we wished to make use of the tribromethanol only when it was indicated or when we could personally superintend the administration. It is not a drug that can be administered indiscriminately, and only persons directly responsible should take charge. Most of the patients in this series had had previously bad surgical experiences and dreaded this particular operation greatly. Our series may be divided surgically as follows:

Laparotomies .....	11
Plastic on face .....	7
Osteomyelitis .....	1
Thyroidectomies .....	5
Breaking up of post-traumatic adhesions in shoulder joint .....	1
	<hr/> 25

A local anesthetic in conjunction with the tribromethanol for a plastic operation was not entirely satisfactory because the patient was narcotized to such extent that coöperation was poor and not sufficiently narcotized to remain absolutely quiet. Other patients who had plastic operations were anesthetized with ether, a very small amount only being needed to keep them quiet. Two patients had two operations each with tribromethanol and both were very enthusiastic about it. The remaining operations were supplemented with nitrous oxid and oxygen, and of these, two (laparotomies) needed a very small amount of ether also, when the exploration was done. All but one patient were fully conscious within six to seven hours after the injection was made; many were conscious in a much shorter time. The one exception was a patient who slept for fifty-six hours postoperatively, during which time she could be aroused to take water and answer questions, but she said she recalled nothing from the time of the injection until fifty-six hours later. No ill effects were noted from this protracted sleep.

This patient later returned to the hospital complaining of paralysis, and was thoroughly examined by the neurological and medical staff with a final diagnosis of hysteria. Possibly her long sleep and semi-consciousness were partly the result of her general nervous reaction.

The average patient having been given his dosage of tribromethanol at 8 a. m. would become drowsy within ten minutes and drop off into a rather deep sleep, from which he could be aroused somewhat by painful stimuli. The nitrous oxid-oxygen or ether would be started about 8:30 a. m.; the operation following immediately would then be finished in the neighborhood of 10 a. m., gas mask removed, the patient would seem to waken normally and talk rationally, but on the following day when questioned would say that he remembered nothing from the time of injection until about 2 o'clock in the afternoon. With the smaller dosage and the more rapid awakening from the deep sleep, patients did not experience the freedom from postoperative pain that the European clinicians report. It was necessary to use morphin to control this pain in some instances. This was probably due both to the smaller dosage of tribromethanol used and to the fact that no morphin was given preoperatively. We still feel, however, that the morphin should not be given before operation and that the tribromethanol should have its effect alone, and that after its effectiveness is over, morphin or lesser sedatives may be indicated.

One patient in our series died sixty hours postoperatively of massive pulmonary atelectasis. She had a cholecystectomy and at operation many adhesions were found in the upper abdomen from a previous laparotomy. She regained consciousness from the tribromethanol and developed signs of lung collapse. In spite of postural treatments and carbon dioxid administrations, she died.

From literature concerning the action of tribromethanol we could not feel that the drug was the cause of death.

#### DISADVANTAGES OF ADMINISTRATION

Granted its limitations and contraindications, in certain diseases there are further disadvantages in its general use. There are decided disadvantages in the calculation of dosage by body weight alone, for one person sleeps for fifty-six hours on a dosage of 90 milligrams per kilogram, another does not appear to sleep at all on the same dosage. Still another dies in thirty minutes with a dosage of 100 milligrams<sup>3</sup> per kilogram and another one dies with a dosage of 125 milligrams per kilogram,<sup>2</sup> while there are many successful administrations recorded with a dosage of 175 milligrams per kilogram. With such a discrepancy in results one must proceed with great care and we feel should not exceed the dosage of 90 milligrams per kilogram. In addition to this the detail and care in its preparation limit its use to the one or two individuals responsible. It works out very satisfactorily for the first operation in a morning, but in a large operative clinic, with case following case in rapid succession, the administration of tribromethanol is too time-consuming, a half-hour at least being necessary to prepare the dosage, inject the drug and bring the patient to the operating room. Its application I think will be limited to those nervous patients who require special care and will not become a routine procedure for every surgical patient.

#### SUMMARY

In conclusion we found: That all fear of the operating room was eliminated. That even though some of the patients did not actually fall into a deep sleep, they remember nothing after the injection of the drug. That there was a deeper relaxation of the patient than with other usual preoperative drugs. That in the patients when ether was used with tribromethanol a very small amount only was needed to maintain the proper level of anesthesia. That when nitrous oxid oxygen was used, a very high percentage of oxygen could be maintained and the patients kept pink, while they were sufficiently relaxed for gall bladder, gastric and pelvic surgery, and that only two patients required the addition of ether to the nitrous oxid-oxygen sequence. That because tribromethanol does not affect the heart and that a high percentage of oxygen can be used in nitrous oxid-oxygen mixture and that the patients are never cyanosed, it can be of great value in anesthetizing thyroid patients and patients with myocardial damage. That great care must be used in preparation of the dosage of the drug. That with the dosages used no untoward effects were noted on the blood pressure or respiration. That the patients were unanimous in agreeing that it was the best surgical experience they had ever had.

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## HAY FEVER PLANTS OF UTAH

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DURING the past year a rather complete survey of the hay fever plants of Utah was made. This was done in order to have a comprehensive knowledge of such plants, the seasons of pollination, and their general distribution. Incidentally, collection of pollens was made of the more important plants.

A wide variation of plants was found—from those in the rather moist valleys of the northern part of the state to the more arid country in the south. Saline soils in the region about Great Salt Lake have a plant life adapted to those conditions. For this reason, Great Salt Lake Valley has the greatest variation of plant life of any valley in the state.

Altitude is also an important factor in distribution. Because of the great variations in altitude throughout the state, there is also a great variation in the plant population. Some of the valleys in the southern part of the state, because of their altitude, have a flora similar to that in the northern part.

## THREE MAIN GROUPS OF UTAH HAY FEVER PLANTS

Many of the plants observed are relatively unimportant in the production of hay fever, but when present in sufficient quantity they undoubtedly produce symptoms in susceptible persons.

Three general divisions might be made of hay fever plants:

1. Trees and shrubs and willows in the spring.
2. Grasses in late spring and early summer.
3. Weeds, sage and rabbit brush, etc., in late summer and fall.

In Group 1, the most important is box elder. Due to numerous box elder trees throughout the

state, hay fever from this tree is rather common. Also, the pollen itself seems to cause symptoms more readily than does pollen from such trees as the ash, cottonwood, and willow. The season is from early in April into the first part of May.

In Group 2, orchard grass, June or blue grass, timothy, salt grass, and redtop—in order—are probably the more important. The season starts in May and extends into July for certain ones, being somewhat longer than that of the trees, but is usually equally severe.

Group 3 is the most important of the three divisions. This group includes such plants as Russian thistle, sagebrush, common ragweed, pickle weed, etc., named in order of their importance. This group has a season, starting in May with four-winged saltbush (*Atriplex canescens*) and ending with the common sagebrush (*Artemisia tridentata*) in September and October. Greasewood (*Sarcobatus vermiculatus*), although not important as a hay fever plant, pollinates during the latter part of May, all of June and July, and the first part of August.

Fruit trees undoubtedly cause a certain amount of trouble. Due to the short season, however, unless the symptoms are very severe, symptomatic treatment is preferable. Should the person be sensitive to some other pollen, the extract from the fruit tree pollen could easily be included in the treatment.

Dandelion (*Taraxacum officinale*) causes rather severe hay fever in a few individuals, particularly such persons as gardeners, farmers, etc., who come into very close contact with the plant. The pollen grain is very sticky and requires that a person be in rather close contact with the plant in order for it to produce symptoms.

Swamp grasses (*Carex spp.*), cat-tail (*Typha latifolia*), bulrush (*Scirpus spp.*), form a group which pollinates heavily but seems to cause very little hay fever.

Such plants as the dock, mustard, bee plant, and clover, although common, cause very little trouble. Rabbit brush has a rather sticky pollen which blows about very little, and is not a great factor in hay fever production in most parts of the state.

The ragweed (*Ambrosia elatior*), although causing severe symptoms in some patients, is not the important hay fever plant that it is in the Middle West.

Alfalfa (*Medicago sativa*), white sweet clover (*Melilotus alba*), and yellow sweet clover (*Melilotus officinalis*) have blossoms in which the pollen is enclosed, as in the sweet pea. They cause hay fever due to the dust they produce when dry and used as hay, the same as any dust will produce symptoms in hay fever patients. It may be, however, that in the dry and pulverized state, the blossoms liberate their pollen and produce hay fever in susceptible persons.

Sagebrush (*Artemisia tridentata*) and Russian thistle (*Salsola pestifera*) are the two worst late summer and fall hay fever plants. The pollination seasons are long, the plants are abundant